

REMARKS**I. THE CLAIMED SUBJECT MATTER**

The above-captioned application discloses and claims a method for affecting the survival or function of neurons through the administration of nucleic acid molecules encoding bioactive truncated GDNF protein products. The present invention is based on the unexpected discovery that truncated forms of the mature GDNF protein as disclosed by Lin et al., in U.S. Patent Application Serial No. 08/182,183 exhibit better bioavailability and retain neurotrophic activity sufficient to promote the survival and growth of dopaminergic neurons.

II. CLAIM STATUS

Claims 31, 32, and 45 to 49 remain pending. Claims 32 and 46 to 49 are hereby cancelled and Claims 31 and 45 are hereby amended.

III. EXPLANATION OF THE AMENDMENTS

The foregoing amendments are fully supported in the specification as originally filed and do not add new matter.

The present amendment cancels claims 32 and 46-49 as they were withdrawn from examination by the Examiner according to 37 C.F.R. § 1.142(b). It is noted herein for the record that the subject matter of the non-elected claims 32 and 46-49 is not being abandoned but will instead be pursued in a duly filed divisional applications. Accordingly, Applicants hereby preserve the right to pursue these cancelled claims in another application(s).

Claims 31 and 45 were amended to include a truncated GDNF polypeptide variant (Ser-Pro²³-Ile¹³⁴; SEQ ID NO:51) specifically disclosed in the specification into the Markush group of the claims.

Claim 45 was also amended to include another specifically identified sequence (SEQ ID NO:24) into the Markush group of that claim.

1. Support for Amended Claims

The requested amendments to claims 31 and 45 with respect to the inclusion of the Ser-[Pro²³-Ile¹³⁴] (i.e., SEQ ID NO:51) species into claims 31 and 45 find support throughout the specification as originally filed, and in particular on page 5, line 19. The amendment to claim 45 with respect to the inclusion of SEQ ID NO:24 into the Markush group also finds support throughout the specification, and in particular on page 5, line 35. The amendment to claim 31 with respect to the replacement of the term “affecting” with “promoting” and the insertion of the term “dopaminergic” to modify the term “neuron” finds support in the specification on page 60, lines 1-3.

2. Support for Amended Specification

The Sequence Listing was amended to include SEQ ID NO:51. The amendment to the Sequence Listing is supported in the specification at page 5, line 19.

IV. CLAIM REJECTIONS AND PATENTABILITY ARGUMENTS

A. The Rejections Under 35 U.S.C. § 112, first paragraph

1. Transitional phrase of Claims 31 and 45

Claims 31 and 45 were rejected under 35 U.S.C. § 112, first paragraph for allegedly containing subject matter “which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention (Office Action, page 3, paragraph 2). In the Office Action, the Examiner also suggested that amending the claims to “administering a polynucleotide consisting of a polynucleotide sequence . . .” may obviate this rejection (Office Action, page 3, paragraph 2). Applicants have amended claim 31 and therefore, dependent claim 45, to include the transitional phrase “consisting of a polynucleotide sequence” as suggested by the Examiner.

Claims 31 and 45 were also rejected under 35 U.S.C. § 112, first paragraph, allegedly, because the specification, while being enabling for a method of increasing survival of dopaminergic neurons with structurally defined GDNF polypeptides, does not reasonably provide enablement for any *in vivo* method for increasing survival of unknown populations of neurons with structurally uncharacterized GDNF

polypeptides using gene therapy. The Examiner supports this allegation largely by claiming that “no description of successfully using gene therapy to accomplish [increasing survival of dopaminergic neurons or increasing dopamine uptake] . . . is disclosed, nor known in the art (Office Action, page 5, lines 3-4) .”

Applicants respectfully traverse Examiner’s allegation that claims 31 and 45 fail to meet the requirements of 35 U.S.C. § 112, first paragraph. First, Applicants note that the controlling legal precedent requires that the USPTO must accept the objective truth of Applicants’ teachings of enablement unless there is a reason to doubt these teachings:

As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must be taken as in compliance with the enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.** Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the teaching contained in the specification is truly enabling. [emphasis in original]

***In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971).**

Under *Marzocchi* therefore, the present specification must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is reason to doubt the objective truth of Applicants’ teachings of enablement. Applicants also note that under *Marzocchi*, the Examiner is required to provide acceptable evidence or reasoning to back up its assertions regarding lack of enablement under 35 U.S.C. 112, first paragraph:

In any event, it is incumbent upon the **Patent Office**, whenever a rejection on this basis is made, **to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.** Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure. [emphasis in bold added]

***Marzocchi* at 370.**

Regarding Examiner's comments in lines 3-4 at page 5 of the outstanding Office Action relating to the alleged lack of any "description of successfully using gene therapy [to increase survival of dopaminergic neurons]", Applicants respectfully direct the Examiner's attention to the enclosed prior art publication describing the use of gene therapy in rats to increase survival of dopaminergic neurons from degeneration induced by the neurotoxin 6-hydroxydopamine (see, Bohn *et al.*, *Science*, vol. 275, 7 February 1997). In accordance with *Marzocchi*, Bohn *et al.* represents suitable proof that the teachings contained in the specification is truly enabling when considered with that known in the art at the time of filing the present application.

Applicants have provided sufficient evidence to rebut the Examiner's allegation that the claimed methods to increase the survival of dopaminergic neurons are not enabled by the present specification. In addition, the present rejection fails to supply the requisite evidence or specific technical reasoning required to meet the requirements of *Marzocchi*. Therefore, Applicants respectfully assert that the present rejection must be withdrawn as being improper.

In support of the present rejection of claims 31 and 45 under 35 U.S.C. § 112, first paragraph, the Examiner also relied heavily on the fact that the Applicants did not "provide even a single *in vivo* working example of the claimed method" but rather "extrapolated from the limited *in vitro* tissue cultures disclosed using 15 day old embryonic rat substantia nigra neurons. (Office Action, page 6, lines 4-7). Applicants respectfully assert that neither 35 U.S.C. 112, first paragraph, nor any other section of the Patent Statute or Patent Rules, requires that a specific working example be disclosed if the invention is otherwise disclosed in such manner that one skilled in the art would be able to practice the invention without undue experimentation. *In re Borkowski*, 164 USPQ 642, 645 (CCPA 1970); *Ex parte Nardi*, 229 USPQ 79, 80 (BPAI 1986); MPEP 2164.02. Applicants submit that the teachings in the specification, combined with that which was known in the art at the time the application was filed, sufficiently disclose how to make and use the present invention in such a manner that one skilled in the art would be able to practice the same without undue experimentation, and that no working example is necessary, consistent with the requirements of *Borkowski*, *Nardi*, and MPEP 2164.02.

The Examiner's rejection presents nothing to rebut the evidence and arguments provided here in support of the enablement of the claimed invention. Applicants assert that the evidence favors enablement of the claimed invention by the specification and that which would have been known to one skilled in the art at the time the present application was filed, especially in view of the burden on the Patent Office to

prove otherwise. In view of the foregoing, Applicants submit that this aspect of the present rejection is **legally improper**, and should be withdrawn. Such action is requested.

Claims 31 and 45 were also rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. More specifically, the Examiner alleges that the metes and bound envisioned by the recitation "function of neurons" to be "affected" was indefinite. Although Applicants respectfully disagree with the Examiner's position, Applicants have amended claims 31 and 45 to remove the basis for Examiner's allegation that claims 31 and 45 are indefinite, solely for purposes of advancing the case to issuance.

CONCLUSION

Applicants respectfully assert that the previously described rejections of claims 31 and 45 under 35 U.S.C. § 112, first and second paragraphs have been rendered moot on the basis of the foregoing amendments and remarks, therefore, the rejections should be withdrawn.

Respectfully submitted,



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